REMARKS

The Examiner rejected Claims 1, 2, 4-9, 12, 13 and 15-20 under 35 U.S.C. 103(a) as obvious over Alberts et al. (U.S. Patent No. 6,204,064) in view of Douglass et al. (U.S. Patent No. 6,151,405). Claims 3, 10, 11, 14, 21 and 22 stand rejected as unpatentable over Alberts and Douglass and further in view of Anderson et al. (U.S. Publication 2003/0032017).

As disclosed in the applicant's specification of the present invention (see Paragraphs 3 and 8), the Alberts patent describes a method for measuring quantitatively the progression of a lesion toward malignancy by digitizing the images of clinical samples and analyzing nuclear chromatin texture features in the nuclei captured in the images. Numerical values are assigned to these features and compared to a monotonic progression curve previously established using the same criteria on known clinical samples ranging from normal to malignant tissue. Thus, the procedure provides a quantitative assessment of the condition of the tissue as well as a method for testing the efficacy of chemo preventive drugs or therapeutic treatments. That is, the physician is provided with information representative of a result formulated by the analytical algorithm built into the diagnostic system (e.g., a numerical value assigned to the nuclear signature calculated by the system and a resulting position in the progression curve). However, the physician is not provided with a tissue image that has been information-enriched by the system and made available for visual inspection as an aid toward improved diagnostic evaluation. As a result, the unique training and ability of pathologists to interpret visual imagery are not exploited beyond the prior art.

The applicant's advance over the technique described in the Alberts patent, of which the applicant is a co-inventor, lies in the fact that it provides information-enriched images of the tissue of interest in addition to the quantitative, numerical information generated by the analytical algorithm. Such a system enables the pathologist to study histometric and karyometric features that are not visually detectable in the images of the stained sample acquired by the optical system but are rendered visible by the system's image-enhancing algorithms. Thus, significant chromatin texture features that otherwise would escape visual inspection of the stained tissue become available for evaluation by the physician, in addition to the numerical evaluation taught by Alberts. It is noted that these features are not enhanced images of the colors resulting from the staining of the tissue. Rather, they are visual identifiers of otherwise invisible optical-density information that the analytical algorithm of the diagnostic system determines to be associated with chromatin texture features of interest.

The Douglass patent describes a mechanized system for evaluating the amount of marker-identifying precipitate present in each pixel of the image of a cellular specimen. The invention involves fixing and staining a cellular specimen conventionally to produce a colored insoluble precipitate that identifies the marker of interest (such as the presence of alkaline as a marker for a trisomy 21 fetus); obtaining a magnified color image of the specimen; identifying an object (area) of interest within the image; and evaluating the amount of visually detectable marker-identifying precipitate in the object of interest. This last step is the essence of the invention and involves identifying a centroid for an object of interest, computing a color ratio for each pixel in an area around the centroid, computing an average color ratio for all pixels in such area having a ratio greater than a predetermined threshold, and comparing the computed average color ratio to an intensity threshold to evaluate the amount of marker-identifying precipitate in the area. In essence, the invention identifies whether or not the intensity of a particular color in a

given cell of the sample is sufficiently high to reliably indicate that the marker is present in the cell.

Thus, the invention is directed at improving the ability to discriminate between colors in the stained tissue in order to identify candidate objects of interest. That is, the invention provides a degree of color discrimination that is beyond what is possible by visual inspection. The mechanized process is based on an analysis of the colors present in the stained sample, no more. It does not highlight chromatin features that have been identified as statistically significant through an analysis of optical density information. The processing performed by the system evaluates color, shape and size of the cell nucleus of each of the candidate objects in order to eliminate objects not likely to contain the marker-identifying precipitate, not to highlight invisible chromatin features. See col. 6, lines 51-53, and col. 8, lines 19-23. In approach, the Douglass invention is like Alberts': it analyzes the image captured by the microscope to produce a number; then it uses the number to produce a result (a position along a progression curve in Alberts' case; an indication of the presence of a marker in Douglass' case). Neither displays the new information via an enhanced image.

With respect to independent Claims 1 and 12, the Examiner found that it would have been obvious to modify the teachings of Alberts ('064) and use a visually detectable marker as taught by Douglass ('405) in order to meet the limitation of "assigning a visually detectable marker to each of said portions of the image corresponding to image-forming signals that produced said measure," as recited in the applicant's claims. The applicant respectfully submits that the claims are not rendered obvious by the combination of the two referenced patents.

When dealing with an obviousness rejection, it is well settled that to establish a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Without a motivation to combine, the skill of the artisan, by itself, cannot be relied upon in hindsight to provide the suggestion to combine references. That is, the teaching or suggestion to make the claimed combination must be found in the prior art, not in the applicant's disclosure. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. Furthermore, the prior art references when combined must teach or suggest all the claim limitations. (MPEP §§ 2132,2143)

Inasmuch as the "image-forming signals" of the applicant's claims are optical-density, this additional limitation has been added to all pending claims. Neither Alberts nor Douglass teaches or suggests highlighting with a visually perceptible marker (which may or may not be color) the results of a statistical analysis of optical density information. This is the advance over Alberts brought to the art by the present invention. Douglass simply teaches an algorithm to discriminate among colors. There is nothing in it suggesting using a marker to render visible the statistically significant chromatin features identified by the Alberts technique on the basis of optical-density information.

In addition to the lack of suggestion or motivation, it is important to note that the teachings of these two references, in combination, would not produce the claimed

invention. As mentioned, the Douglass patent does not describe assigning a visually detectable marker to portions of the tissue image based on image-forming signals that produced a measure of features that is a statistically significant indicator of pathology, as claimed. The patent describes a related but separate process, that of improving discrimination among the colors present in the stained tissue; but it does not deal with new statistically significant information that may be present in the colors. The marker is added to the tissue, not the image. Thus, to achieve the result of the present invention, one skilled in the art would have to provide the additional knowledge required to appropriately modify the teachings of the references. However, the existence of that knowledge is not sufficient to establish a *prima facie* case of obviousness without some objective reason even to combine the teachings of the references (MPEP § 2143.01), and no such reason is provided by the references or otherwise in this case.

Moreover, while the ordinary skill of the artisan coupled with objective reasons to combine may be invoked to support a finding of obviousness in the combination of prior art, it may not be invoked to supply elements of the invention that are missing in the combination. As discussed, the concept of converting the statistical information generated by the Alberts technique into visual information that the pathologist can use to improve its subjective diagnosis is totally missing in the teachings of these two references.

Therefore, the applicant respectfully submits that Alberts and Douglass do not suggest their combination or modification to arrive at the present invention; no objective reason to combine or modify them exists because Douglass deals with a separate problem; and in any event their combination would not produce the claimed invention. Therefore, the

basic requirements for a *prima facie* case of obviousness of amended independent Claims 2 and 13 are not believed to be present.

The same reasoning applies to the rejection of all dependent claims, with the further points of distinction provided by the particular limitations added by each claim. For example, contrary to the Examiner's finding, the array microscope of Claims 9, 11, 20 and 22 is not mentioned in any way in the Alberts reference. Such a microscope, which is the most suitable microscope for practicing the present invention, had not yet been developed at the time of the Alberts disclosure. As referenced in Paragraphs 10-14 of the specification of the present invention, such novel microscope was first described in International Application PCT/US02/08286, which was based on a provisional application filed in 2001. Therefore, the combination of Alberts and Douglass could clearly not produce the inventions of Claims 9, 11, 20 and 22.

With respect to Claims 3, 10, 11, 14, 21 and 22, the Examiner cited an additional references, the Anderson publication, for disclosing a process for the quantification of low molecular weight and low abundance proteins that includes information-enriched images. In fact, this reference describes images of enriched proteins, not enriched images. (See referenced Paragraph 48.) Therefore, it is respectfully submitted that this reference does not provide any disclosure relevant to the present invention.

In view of the foregoing, the applicant believes that his invention represents an advance in the art that is characterized by novel and non-obvious features that are worthy of patent

protection. Accordingly, reconsideration of the rejection of the pending claims, as amended, is respectfully requested.

No fee is believed to be due with this response. However, should any payment be required, please charge it to our Deposit Account No. 04-1935.

Respectfully submitted,

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